

### REMARKS

In response to the Office Action mailed March 17, 2006, Applicants canceled claims 9-11, 17, 31 and 32, and added new claims 35 and 36. Claims 12, 16, 20, 21, 24, 26, 33 and 34 have been amended. Support for the amendments and the new claims can be found throughout the specification. For example, support for amended claims 12 and 20 can be found at least at pages 8-9, ¶¶[0028] and [0029]. No new matter has been added by the amendment. Claims 12-24, 26, 27 and 33-36 are presented for examination.

Applicants wish to extend their appreciation to the Examiner for his time and consideration during the telephone interview of June 15, 2006, with Applicants' representative, Allyson Hatton. During the interview, various strategies for overcoming the outstanding rejections were discussed. In particular, the discussion included possible alternative claim language to remove the word "using" from claims 12 and 20 to overcome the rejections for lack of written description and enablement, and as allegedly being anticipated by or obvious in view of Tang *et al.* The cancellation of claim 9, and the amendment of claims 12, 16, 20, and 24 to recite BACE instead of APP binding protein were also discussed as strategies to overcome the written description and enablement rejections. The addition of steps to claims 12 and 20 were discussed as strategies to overcome the rejection of the claims under 35 U.S.C. § 103 as being unpatentable over (i) Sauder *et al.* in view of Anderson *et al.*, and (ii) Balaji *et al.* in view of *In re Gulack*. The amendments and arguments presented below are consistent with those discussed with the Examiner, and are also consistent with the Examiner's comments in his Interview Summary dated June 21, 2006.

#### 35 U.S.C. § 112, first paragraph

*Written Description.* The Examiner maintained the rejection of claims 9-27 and rejected new claims 31-34 under 35 U.S.C. § 112, first paragraph for failing to satisfy the written description requirement<sup>1</sup>. The Examiner states

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<sup>1</sup> Claims 9-11, 17, 25, 31, and 32 have been canceled, so the rejection of these claims for failure to meet the written description requirement should be withdrawn.

the genus of 3-D models of BACE or APP binding proteins encompasses species that are *widely* variant. It is noted that the genus of 3-D models of BACE or APP binding proteins are generated *using* the '*relative structural coordinates*' as '*represented in*' Figure 1 or specific amino acid positions thereof. Because the 3-D model is generated '*using*' structural coordinates, the claims have been interpreted in accordance with MPEP 2111 as including any homology model of BACE or an APP binding protein having any structure. See Office Action at page 4 (emphasis in original).

Applicants do not concede that the Examiner's position is appropriate. However, to further prosecution, claims 12 and 20 have been amended, such that the three dimensional model of an active site of BACE is not generated by *using* the relative structural coordinates of Figures 1A-1EEE, but rather the three dimensional model *comprises* the relative structural coordinates according to Figures 1A-1EEE of amino acids of ¶[0031] (see claim 12 and the specification at page 9) a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, or ¶[0032] (see claim 20 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

The Examiner also quotes page 6, ¶[0021] of the specification as stating "...it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of FIG. 1." See Office Action at page 4. The Examiner interprets this passage as meaning that, "'relative structural coordinates' are not limited to those disclosed in Figure 1, but can be *any* structural coordinates." See Office Action at page 4 (emphasis added). Applicants respectfully disagree with the Examiner's conclusion.

Page 6, ¶[0021] of the specification says: "The structural coordinates of the present invention may be modified from the original set provided in Figure 1 by mathematical manipulation, such as by inversion or integer additions or subtractions. *As such*, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of FIG. 1." (Emphasis added). Thus the coordinates of Figure 1 cannot be *any* structural coordinates. They can be the coordinates of Figures 1A-1EEE,  $\pm$  a root mean square deviation from the backbone atoms of BACE of not more than 1.5 Å, or

coordinates modified from those of Figures 1A-1EEE by mathematical manipulation. Such coordinates are predictable and do not change the resulting structure represented by the original coordinates. Contrary to the Examiner's conclusion, the genus of 3-D models of BACE or APP binding proteins encompassed by the claims is not widely variant, and the written description requirement is satisfied in this regard.

The Examiner also states that claims 16, 19, 24, and 27 involve steps of contacting the agent with BACE or an APP binding protein optionally in the presence of APP and optionally to determine the effect of the agent on BACE or the APP binding protein. The Examiner further asserts that "[t]he specification discloses only a single species of BACE polypeptides or APP binding proteins, *i.e.*, SEQ ID NO:1, and discloses only a single species of APP proteins, *i.e.*, SEQ ID NO:2. Other than this single species of the genus of BACE or APP polypeptides, the specification fails to disclose any other representative number of species, which encompasses widely variant species of polypeptides." See Office Action at page 6.

As amended, claims 16 and 24 recite BACE, and not APP binding protein. Applicants disagree that the genus of BACE (see claims 16 and 24) and APP polypeptides (see claims 19 and 27) encompasses widely variant species of polypeptides. "BACE" is defined in the specification at page 5, ¶[0016], as

the  $\beta$ -secretase enzyme that cleaves  $\beta$ -amyloid precursor protein (APP) at residue 671...The amino acid sequence of BACE preferably has the amino acid sequence deposited with Swiss Prot under accession number P56817 (SEQ ID NO:1), including conservative substitutions. As used herein, BACE also includes "BACE peptides," which are molecules having less than the complete amino acid sequence of BACE. Preferably BACE peptides include the active site in which BACE binds to and cleaves APP. Most preferably, the BACE peptide corresponds to amino acid residues 58-447 set forth in Figures 1A-1EEE ("BACE<sub>58-447</sub>"), including conservative substitutions. See also the Reply to Office Action submitted April 26, 2005, at pages 2-3.

"APP" is defined in the specification at page 5, ¶[0017], as " $\beta$ -amyloid precursor protein having the amino acid sequence deposited with Swiss Prot under accession number CAA31830,

including conservative substitutions. Preferably, APP peptides include the active site in which APP is cleaved by BACE.”

As the Federal Circuit stated in Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005):

The ‘written description’ requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor’s obligation to disclose the technological knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed...The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.

The Court in Capon further stated:

Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. *Id.* at 1359.

In view of the disclosure in the specification, and the existing knowledge in the field of protein biology, one would understand the meaning of BACE and APP as recited in claims 16, 19, 24, and 27. Applicants therefore request reconsideration and withdrawal of the rejection for lack of written description under 35 U.S.C. § 112, first paragraph.

*Enablement.* The Examiner maintained the rejection of claims 9-27 and rejected new claims 31-34 under 35 U.S.C. § 112, first paragraph for failing to satisfy the written description requirement<sup>2</sup>. In *In re Wands*, 858 F.3d 731 (Fed. Cir. 1998), the United States Court of Appeals for the Federal Circuit described the factors to be considered and balanced when determining whether a disclosure satisfies the enablement requirement. Applicants discussed these factors in

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<sup>2</sup> Claims 9-11, 17, 25, 31, and 32 have been canceled, so the rejection of these claims for failure to meet the enablement requirement should be withdrawn.

the reply submitted April 26, 2005! The Examiner disagreed with Applicants' comments regarding several of these factors, which are addressed below.

*Breadth of the claims.* The Examiner states that "the breadth of the claims are so broad as to encompass the use of all 3-D models of BACE or APP binding proteins that are generated using the 'relative structural coordinates' as 'represented in' Figure 1 or specific amino acids positions thereof." See Office Action at page 7 (emphasis in original). Applicants do not concede that the Examiner's position is appropriate. However, to further prosecution, claims 12 and 20 have been amended such that the three dimensional model of an active site of BACE is not generated by using the relative structural coordinates of Figures 1A-1EEE, but rather the three dimensional model *comprises* the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031] (see claim 12 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, or of ¶[0032] (see claim 20 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å. The Examiner also states that "according to the specification, 'relative structural coordinates' are not limited to those disclosed in Figure 1, but can be any structural coordinates." See Office Action at page 7. Applicants respectfully disagree with the Examiner's conclusion.

Page 6, ¶[0021] of the specification says: "The structural coordinates of the present invention may be modified from the original set provided in Figure 1 by mathematical manipulation, such as by inversion or integer additions or subtractions. *As such*, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of FIG. 1." (Emphasis added). Thus the coordinates of Figure 1 cannot be *any* structural coordinates. They can be the coordinates of Figures 1A-1EEE,  $\pm$  a root mean square deviation from the backbone atoms of BACE of not more than 1.5 Å, or coordinates modified from those of Figures 1A-1EEE by mathematical manipulation. Such coordinates are predictable and do not change the resulting structure represented by the original coordinates. Contrary to the Examiner's conclusion, the genus of 3-D models of BACE or APP

binding proteins encompassed by the claims is not widely variant, and the scope of the claims are no broader than Applicants' contribution.

Regarding active sites, the Examiner states that "the active site is not limited to those residues disclosed in the specification at p. 9, ¶¶[0031] to [0032], but to *any* region of any 3-D structure as noted above that 'favorably interacts or associates with another agent.'" See Office Action at page 8 (emphasis added). Applicants do not concede that the Examiner's position is appropriate. However, to further prosecution, claims 9-11 have been canceled, claim 12 as amended is directed to a three dimensional model of an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031] (see claim 12 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, and claim 20 is directed to a three dimensional model of an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0032] (see claim 20 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å. The scope of Applicants' claims are no broader than Applicants' contribution.

Regarding claims 16, 19, 24 and 27, the Examiner states that "[t]he claims encompass the use of any BACE, APP binding protein, or APP polypeptide having any sequence of amino acids." See Office Action at page 8. "BACE" is defined in the specification at page 5, ¶[0016], as

the  $\beta$ -secretase enzyme that cleaves  $\beta$ -amyloid precursor protein (APP) at residue 671...The amino acid sequence of BACE preferably has the amino acid sequence deposited with Swiss Prot under accession number P56817 (SEQ ID NO:1), including conservative substitutions. As used herein, BACE also includes "BACE peptides," which are molecules having less than the complete amino acid sequence of BACE. Preferably BACE peptides include the active site in which BACE binds to and cleaves APP. Most preferably, the BACE peptide corresponds to amino acid residues 58-447 set forth in Figures 1A-1EEE ("BACE<sub>58-447</sub>"), including conservative substitutions. See also the Reply to Office Action submitted April 26, 2005, at pages 2-3.

“APP” is defined in the specification at page 5, ¶[0017], as “β-amyloid precursor protein having the amino acid sequence deposited with Swiss Prot under accession number CAA31830, including conservative substitutions. Preferably, APP peptides include the active site in which APP is cleaved by BACE.”

The Federal Circuit Court in Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1361 (Fed. Cir. 1998) stated: “The enablement requirement is met if the description enables any mode of making and using the invention.” The Federal Circuit Court also stated in Invitrogen Corp. v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005): “[e]nablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions.” Applicants assert that the description in the specification of the terms “BACE” and “APP” are described sufficiently in the specification such that the scope of the claims is no broader than Applicants’ contribution.

*State of the Prior Art.* The Examiner asserts that the prior art taught or suggested the claimed methods. The Examiner makes no further comment regarding the prior art with respect to enablement. Applicants address the prior art below with respect to the outstanding rejections under 35 U.S.C. § 102, and 35 U.S.C. § 103, and maintain that no one has previously disclosed or suggested the claimed methods.

*Level of Predictability in the Art.* The Examiner states that

[a]t the time of the invention, methods for displaying a 3-D structure of a polypeptide and generating homology models were known in the prior art...a skilled artisan would have recognized that there was a high level of unpredictability in using altered 3-D protein structures as encompassed by the claims with an expectation that the altered 3-D structures represent a biologically relevant conformation of BACE. See Office Action at page 9.

The claims are directed to, *inter alia*, the use of a three dimensional model of an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031] (see claim 12 and the specification at page 9) ± a

root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, or ¶[0032] (see claim 20 and the specification at page 9) ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å. The claims are not directed to using “altered 3-D protein structures” as stated by the Examiner. The application therefore provides sufficient guidance to allow a skilled artisan to practice the claimed methods with a reasonable degree of predictability.

The Examiner also states that “the claims encompass the use of any BACE, APP binding protein, or APP polypeptide, including mutants and variants, and it is highly unpredictable as to the effects of altering the amino acid sequence of a polypeptide and the resulting effects on the activity of the mutant or variant polypeptide.” See Office Action at page 9. BACE and APP are described in the specification at page 5, ¶¶[0016] and [0017]. In view of the knowledge in the field of protein biology, and in view of the disclosure in the specification, Applicants assert that the claimed methods can be practiced with a reasonable degree of predictability.

*Amount of Experimentation required.* The Examiner states that

[w]hile methods of altering a 3-D structure of a protein *in silico* and methods of mutating a polypeptide's sequence were known at the time of the invention, it was not routine in the art to create a substantial number of altered 3-D structures or polypeptides as encompassed by the claims without guidance as to which of those is useful in accordance with the asserted utility of the claimed invention, i.e., “in rational drug design methods to identify agents that may interact with active sites of BACE” that “may represent new therapeutics.” See Office Action at page 10.

Applicants reiterate that the claims are directed to, *inter alia*, the use of a three dimensional model of an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031] (see claim 12 and the specification at page 9) ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, or ¶[0032] (see claim 20 and the specification at page 9) ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å. The claims are not directed to the creation of substantial numbers of “altered 3-D structures or



polypeptides” as stated by the Examiner. In view of the knowledge in the field of protein biology, and in view of the disclosure in the specification, Applicants maintain that the application therefore provides sufficient guidance to allow a skilled artisan to practice the claimed methods without undue experimentation.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection for lack of enablement under 35 U.S.C. § 112, first paragraph.

35 U.S.C. §§ 102(e)/103(a)

The Examiner maintained the rejection of claims 9-27 and rejected new claims 31-34 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Tang *et al.*<sup>3</sup> The Examiner states that “there is no requirement in the claims that the 3-D structure of BACE or APP binding protein be limited to having the structural coordinates of Figure 1.” See Office Action at page 11. Further, the Examiner states that “the claims encompass the use of 3-D models of BACE or APP binding proteins that are generated *using* the ‘relative structural coordinates’ as ‘represented in’ Figure 1 or specific amino acids positions thereof.” See Office Action at page 11 (emphasis in original). Applicants do not concede that the Examiner’s position is appropriate. However, to further prosecution, claims 12 and 20 have been amended such that the three dimensional model of an active site of BACE is not generated by using the relative structural coordinates of Figures 1A-1EEE, but rather the three dimensional model *comprises* the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031] (see claim 12 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å or ¶[0032] (see claim 20 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

The Examiner also states that “according to the specification, ‘relative structural coordinates’ are not limited to those disclosed in Figure 1, but can be any structural coordinates.” See Office Action at page 12. Applicants disagree with the Examiner’s conclusion.

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<sup>3</sup> Claims 9-11, 17, 25, 31, and 32 have been canceled, so the rejection of these claims under 35 U.S.C. § 102(e) or under 35 U.S.C. § 103(a) should be withdrawn.

Page 6, ¶[0021] of the specification says: "The structural coordinates of the present invention may be modified from the original set provided in Figure 1 by mathematical manipulation, such as by inversion or integer additions or subtractions. *As such*, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of FIG. 1." (Emphasis added). Thus the coordinates of Figure 1 cannot be any structural coordinates. They can be the coordinates of Figures 1A-1EEE,  $\pm$  a root mean square deviation from the backbone atoms of BACE of not more than 1.5 Å, or coordinates modified from those of Figures 1A-1EEE by mathematical manipulation. Such coordinates are predictable and do not change the resulting structure represented by the original coordinates. Contrary to the Examiner's conclusion, the 3-D models of Tang *et al.* do not fall within the scope of recited 3-D models as recited in the claims. Tang *et al.* does not disclose the structural coordinates of Figures 1A-1EEE. For example, the BACE residues included in the Tang crystal (amino acids Ala14 to Thr454) are different than the residues included in Figures 1A-1EEE (amino acids Thr47 to Tyr460 plus nine extra residues due to a cloning artifact) (numbering of amino acids is according to Applicants' specification). See Tang, col. 18, lines 31-34 and col. 29, lines 35-39, and Applicants' specification at page 14, ¶[0041] and page 15, ¶[0045] (note that in col. 18 of Tang, the numbering of amino acid residues is according to SEQ ID NO:3 of Tang which numbering corresponds to (n - 2) according to the numbering of the BACE sequence in Applicants' specification). Thus, Tang does not anticipate pending claims 12-16, 18-24, 26, 27, 33 and 34. Furthermore, as making a protein crystal is not trivial, Tang would not have provided one skilled in the art with a reasonable expectation of success in obtaining the coordinates of Figures 1A-1EEE.

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(e) as anticipated by or under 35 U.S.C. § 103(a) as obvious over Tang *et al.*

35 U.S.C. § 103(a)

The Examiner rejected claims 9-19, 21, and 31-33 under 35 U.S.C. § 103(a) as obvious over Sauder *et al.* in view of Anderson *et al.* (US Patent 5,942,400).<sup>4</sup> The Examiner states that “at the time of the invention, it would have been obvious to one of ordinary skill in the art to model the inhibitor of Anderson *et al.* with BACE according to Sauder *et al.*, synthesizing the agent, and screen the agent for its ability to inhibit BACE activity.” See Office Action at page 13. The Examiner characterizes Sauder *et al.* as teaching a method of computer modeling of human BACE with APP and APP mutant substrates to determine the substrate specificity of BACE.” *Id.* The Examiner characterizes Anderson *et al.* as teaching “methods for producing purified human BACE...and using the purified BACE in an *in vitro* screening assay to identify BACE inhibitors.” *Id.* The Examiner then states that “it would have been obvious to one of ordinary skill in the art to model the inhibitor of Anderson *et al.* with BACE according to Sauder *et al.*, synthesize the agent, and screen the agent for its ability to inhibit BACE activity.” *Id.*

Applicants do not concede that the Examiner's position is appropriate. However, claims 12-16, 21, and 33 as amended are directed to providing a crystalline composition comprising Beta-site APP Cleaving Enzyme (BACE), determining the three dimensional structure of BACE, and generating a three dimensional model of an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031] (see claim 12 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å. The model of Sauder *et al.* was generated based on sequence alignment data. Based on Sauder *et al.*, one would not have a reasonable expectation of success of providing a crystalline composition comprising Beta-site APP Cleaving Enzyme (BACE), determining the three dimensional structure of BACE, and generating a three dimensional model of an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031]  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å. As known to those skilled in the art, generating a protein

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<sup>4</sup> Claims 9-11, 17, 31, and 32 have been canceled, so the rejection of these claims under 35 U.S.C. § 103(a) should be withdrawn.

crystal is not a trivial task. Anderson *et al.* also fails to teach how one would practice the claimed methods, and therefore does not make up for the deficiencies of Sauder *et al.*

In view of the foregoing, Applicants request reconsideration and withdrawal of the rejection of claims 12-16, 21, and 33 under 35 U.S.C. § 103(a) as obvious over Sauder *et al.* in view of Anderson *et al.*

The Examiner maintained the rejection of claims 9-15, 17-18, 20-23, and 25-26 and rejected new claims 31-34<sup>5</sup> under 35 U.S.C. § 103(a) as being unpatentable over Balaji in view of *In re Gulack*. In the Office Action dated January 26, 2005, the Examiner stated that "it would have been obvious to one of ordinary skill in the art at the time of the invention to perform rational drug design as taught by Balaji to result in an agent that interacts with BACE, wherein only nonfunctional descriptive material is additionally present in the claims..." See Office Action at pages 20-21.

Applicants do not concede that the Examiner's position is appropriate. However, to further prosecution, the independent claims 12 and 20 have been amended to include the steps of providing a crystalline composition comprising Beta-site APP Cleaving Enzyme (BACE), and determining the three dimensional structure of BACE. Neither Balaji or Gulack, alone or in combination, disclose or suggest such steps, and the claims cannot be said to differ only by the inclusion of nonfunctional descriptive material. Applicants therefore request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 16, 19, 24, and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Balaji *et al.* in view of *In re Gulack* and further in view of Anderson *et al.* The Examiner states that "Anderson *et al.* teaches methods for producing purified human BACE...and using the purified BACE in an *in vitro* screening assay along with APP or fragments thereof to identify BACE inhibitors." See Office Action at page 15. These claims are dependent claims that first require providing a crystalline composition comprising Beta-site APP Cleaving Enzyme

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<sup>5</sup> Claims 9-11, 17, 31, and 32 have been canceled, so the rejection of these claims under 35 U.S.C. § 103(a) as being unpatentable over Balaji in view of *In re Gulack* should be withdrawn.

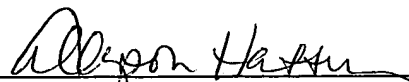
(BACE), determining the three dimensional structure of BACE, and generating a three dimensional model of an active site of BACE, wherein the model comprises the relative structural coordinates according to Figures 1A-1EEE of the amino acids of ¶[0031] (see claim 12 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, or ¶[0032] (see claim 20 and the specification at page 9)  $\pm$  a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å. Neither Balaji *et al.*, *In re Gulack* or Anderson *et al.*, alone or in combination, describe or suggest such methods. For at least the reasons described above, the claims are not unpatentable over Balaji *et al.* in view of *In re Gulack* and further in view of Anderson *et al.*, and Applicants request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Applicants believe the application is in condition for allowance, which action is requested.

Enclosed is a \$120 check for a one month Petition for Extension of Time fee. Please apply any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 16163-015001.

Respectfully submitted,

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Allyson R. Hatton, Ph.D.  
Reg. No. 54,154

Fish & Richardson P.C.  
225 Franklin Street  
Boston, MA 02110  
Telephone: (617) 542-5070  
Facsimile: (617) 542-8906

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